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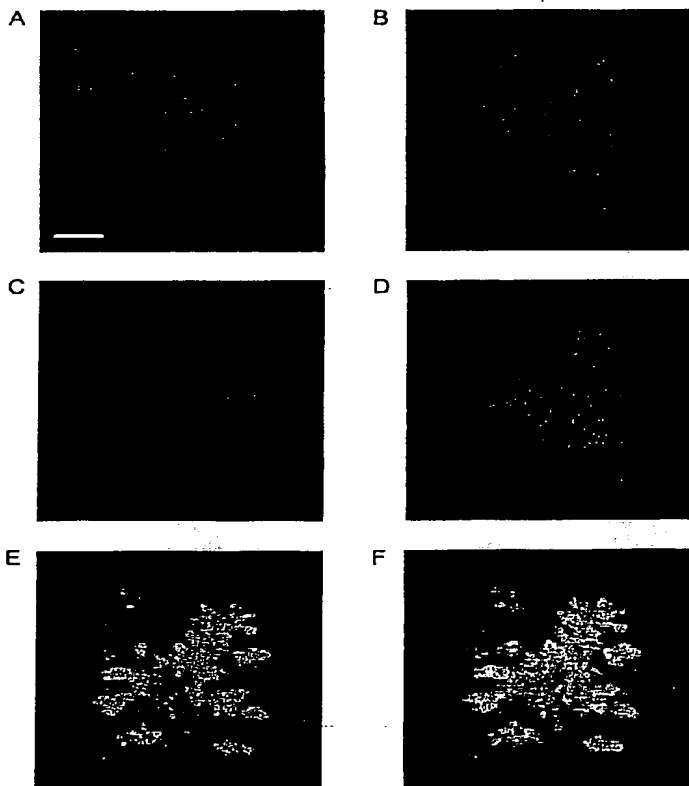
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(54) Title: **METHOD OF MONITORING IMMUNOTHERAPY**



(57) Abstract: The present invention relates to a method of monitoring an immunotherapy against amyloidosis and other diseases characterized by the deposition of abnormal protein aggregates. More specifically, it relates to a method of evaluating an immunotherapy against Alzheimer's disease, based on a novel assay that is characterized by scoring immunoreactivity levels of patient sera in amyloid plaque containing samples. The assay possesses highly predictive properties in relation to the clinical outcome of such an immunotherapy, in contrast to previously used, conventional ELISA assays. Therefore, the novel assay is useful for the evaluation of the efficacy of an immunotherapy in a patient suffering from amyloidosis, particularly Alzheimer's disease.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11413

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 164 295 A (KISILEVSKY ROBERT ET AL) 17 November 1992 (1992-11-17) abstract; claims 1,4	11-15
X	DU Y ET AL: "Reduced levels of amyloid beta-peptide antibody in Alzheimer disease" NEUROLOGY, vol. 57, no. 5, 11 September 2001 (2001-09-11), pages 801-805, XP009026218 ISSN: 0028-3878 abstract page 804, right-hand column, paragraphs 2,3; table 1	1-10

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DODEL RICHARD ET AL: "Human antibodies against amyloid beta peptide: A potential treatment for Alzheimer's disease" ANNALS OF NEUROLOGY, vol. 52, no. 2, August 2002 (2002-08), pages 253-256, XP009026281 ISSN: 0364-5134 abstract page 1	1-10
A	WO 95 20979 A (CERAMI ANTHONY ;ULRICH PETER C (US); VITEK MICHAEL P (US); VLASSAR) 10 August 1995 (1995-08-10) the whole document	1-15
A	WO 01 40261 A (ORTHO MCNEIL PHARM INC) 7 June 2001 (2001-06-07) the whole document	1-15
X	EP 1 172 378 A (DODEL RICHARD DR ;YANSHENG DR DU (US)) 16 January 2002 (2002-01-16) abstract; figure 1 column 4, line 53 - line 58 column 5, line 1 - line 13	1-16
A	WO 02 46222 A (BUCK MARTINA ;CHOJKIER MARIO (US)) 13 June 2002 (2002-06-13) the whole document	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11413

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5164295	A	17-11-1992	NONE	
WO 9520979	A	10-08-1995	AU 692237 B2	04-06-1998
			AU 1870195 A	21-08-1995
			CA 2182731 A1	10-08-1995
			EP 0802797 A1	29-10-1997
			JP 9511492 T	18-11-1997
			WO 9520979 A1	10-08-1995
			US 6410598 B1	25-06-2002
			US 5935927 A	10-08-1999
WO 0140261	A	07-06-2001	AU 1920401 A	12-06-2001
			CA 2393004 A1	07-06-2001
			EP 1233979 A1	28-08-2002
			JP 2003530542 T	14-10-2003
			WO 0140261 A1	07-06-2001
EP 1172378	A	16-01-2002	EP 1172378 A1	16-01-2002
			US 2002009445 A1	24-01-2002
WO 0246222	A	13-06-2002	US 2002137112 A1	26-09-2002
			AU 1982402 A	18-06-2002
			EP 1339743 A2	03-09-2003
			WO 0246222 A2	13-06-2002
			US 2003104488 A1	05-06-2003